

REPLACED BY
PART 54 AMDT

Claims

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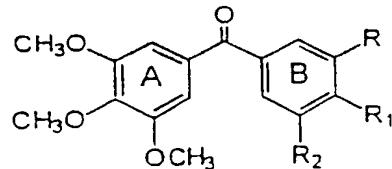
1. The method of synthesizing phenstatin comprising the steps of:
oxidizing 3-(*tert*-butyl dimethylsilyl)oxy-4-methoxybenzaldehyde with
potassium permanganate to form the corresponding carboxylic acid;
5
Sub. B1
converting said carboxylic acid to the corresponding acid chloride;
treating said acid chloride with the lithium derivative obtained from 3,
4, 5-trimethoxybenzene and *t*-butyllithium to form a protected product;
10
and deprotecting said protected product to form phenstatin.

2. The method of synthesizing phenstatin prodrug comprising the steps of:
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phosphorylating phenstatin with dibenzylphosphite in the presence of
bromodichloromethane to form a phosphate ester;
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cleaving the benzyl groups from said phosphate ester by means of
catalytic hydrogenolysis; and
reacting the cleaved phosphate ester with sodium methoxide to produce
the phenstatin sodium phosphate prodrug.

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3. The method of inhibiting cancer cell growth and tubulin polymerization
in an environment inflicted therewith comprising: introducing into said
environment a pharmaceutically acceptable carrier and a small but effective
amount of phenstatin prodrug.

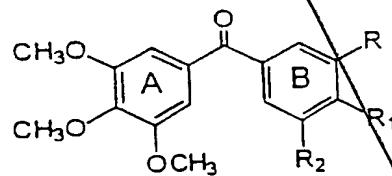
Push A off
5 *B'*

4. Phenstatin prodrugs and derivatives thereof having the structure:



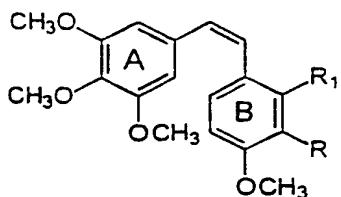
10 wherein when R=H and R₁ = OCH₃, R₂ is OPO₃NA₂, OCOCH₃, H, or OCH₃ and when R=R₂, R₂ is OCH₃, CH₃, CL or F and R₁ is H and when R₁=R₂, R₂ is OCH₃ or OCH₂O and R is H.

15 5. The method of inhibiting human cancer cell growth in a host inflicted therewith comprising administering to said host in pharmaceutically acceptable carrier a small but effective amount of a compound selected from the group consisting of phenstatin, phenstatin prodrug and the derivatives thereof having the structure.



20 25 wherein when R=H and R₁ = OCH₃, R₂ is OPO₃NA₂, OCOCH₃, H, or OCH₃ and when R=R₂, R₂ is OCH₃, CH₃, CL or F and R₁ is H and when R₁=R₂, R₂ is OCH₃ or OCH₂O and R is H.

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1a, R = OH, R₁ = OH

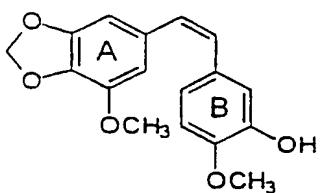
Combretastatin A-1

1b, R = OH, R₁ = H

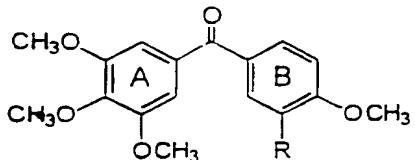
Combretastatin A-4

1c, R = OSi(CH₃)₂C(CH₃)₃, R₁ = H1d, R = OPO₃Na₂, R₁ = H

Combretastatin A-4 prodrug

1e, R = R₁ = H

2. Combretastatin A-2

3a, R = OSi(CH₃)₂C(CH₃)₃

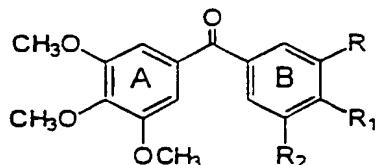
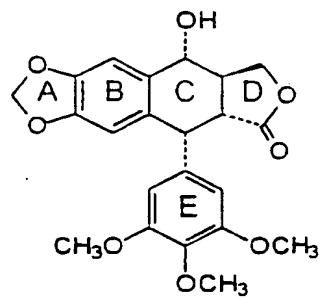
3b, R = OH, Phenstatin

3c, R = OPO₃(C₆H₅CH₂)₂3d, R = OPO₃Na₂

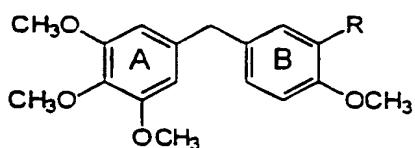
Phenstatin prodrug

3e, R = OCOCH₃

3f, R = H

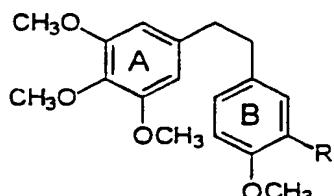
4a, R = H, R₁, R₂ = OCH₂O4b, R = R₂ = CH₃, R₁ = H4c, R = H, R₁ = R₂ = OCH₃4d, R = R₂ = OCH₃, R₁ = H4e, R = R₂ = Cl, R₁ = H4f, R = R₂ = F, R₁ = H

5



7a, R = OH

7b, R = H



8a, R = OH

8b, R = H

Figure 1.